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Neurofibramatosis Type 2 (NF2)

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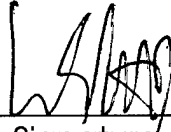
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13. ABSTRACT (Maximum 200 Words) Neurofibromatosis 2 (NF2) is an autosomal disorder characterized by the development of multiple nervous system tumors such as vestibular schwannomas. The purpose of the study is to define the growth rate and clinical course of vestibular schwannomas in NF2-affected individuals. We will develop an international consortium of clinical centers with expertise in NF2, standardize the radiographic analysis of the vestibular schwannomas, assess the patients' audiological functioning, and analyze molecular, pathological, and clinical features of the disease over the course of 3 years. We have enrolled 97% of the target goal of 100 study participants. The difficulty enrolling patients has stemmed from a protracted informed consent approval process and one co-PI leaving a core site. Baseline audiological data and baseline MRI have been collected for 64% and 71% of enrolled subjects, respectively. We have made good progress toward completion of the study's goals and anticipate few problems with the collection of one-year follow-up data.				
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FOREWORD

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PI - Signature


Date

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Introduction

Neurofibromatosis 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All patients inevitably develop bilateral vestibular schwannomas that can lead to total deafness and death if left untreated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to vestibular schwannomas, and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of natural history of vestibular schwannomas, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study is to define the growth rate and clinical course of vestibular schwannomas in NF2-affected individuals. We seek to accomplish this goal through the following steps:

1. Develop an international consortium of clinical centers and expertise in NF2.
2. Develop standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.
3. Analyze standardized prospective neurophysiological/audiological results from NF2 patients.
4. Examination of molecular, pathological, and clinical features which may predict tumor behavior.

This study will lead to a better understanding of the natural history and clinical course of vestibular schwannomas in NF2. The knowledge gained from this study will allow anticipatory guidance of newly diagnosed patients and better recommendations regarding current treatment. The framework of clinical centers, data management, and scientific expertise established during this project will form the core for future studies investigating other aspects of the natural history of NF2 and therapeutic treatment trials in NF2.

Body

STATEMENT OF WORK

Natural History of Vestibular Schwannomas in Neurofibromatosis 2 (NF2)

Task 1. Development of an international consortium of clinical centers and expertise in NF2 and overall project activities.

a. Development of communication infrastructure for NF2 consortium members (month 1); Completed

A complete directory listing the site Co-Principal Investigators, Clinical Coordinators, and other researchers involved in the NF2 study was created and distributed to study members. The directory, which presents phone numbers, fax numbers, addresses, and email addresses, allows study members to communicate with each other when necessary.

b. Development of centralized data management system (months 1-3); Completed

A coordinated system for collecting and transmitting study data was established. A procedure manual documenting all study procedures was established and distributed to all Central Laboratory Centers and Patient Collection Centers.

As detailed in this procedure manual, HEI serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators initially FAX all completed data forms to HEI and later mail all original forms at the end of the month. A Central Tracking System was established at HEI to track each subject and assure the consistent inflow of data from each site.

All study data that are sent by a Patient Collection Center and received by HEI are recorded on the Central Tracking System. Files for each subject have been created and kept in a locked cabinet. A computerized database has been created to house the study data and as the forms are sent to HEI, the data are entered into the database.

c. Development of infrastructure within participating clinical centers to identify and recruit NF2 patients (months 1-3); Completed

A Clinical Coordinator has been identified at each site, and the infrastructure for tracking patients has been established at each Patient Collection Center. The study protocol and the consent forms have been submitted to local Institutional Review Boards at each site for approval. Each Patient Collection Center has an established NF2 database and/or has access to medical records with information on all the NF2 patients followed at their site. These were the basic sources for initial patient screening and identification. HEI submitted articles which were published in widely-read NF2 publications such as the *NNFF Newsletter* and the *NF2 Review*. A summary of the study was posted on several web sites including that of House Ear Institute, the NF2Crew, the National Neurofibromatosis Foundation, CenterWatch, and the National Cancer Institute. HEI continues to receive correspondence from interested NF2-affected individuals and from researchers around the world.

d. Train clinical centers' staff in study protocol (months 1-3); Completed

Clinical centers' staff have been trained in study protocol at the initial Steering Committee Meeting on December 4, 1998. Grant protocol and procedure manual were distributed to each Co-PI and

Clinical Coordinator at each site. HEI maintains ongoing email and telephone correspondence with the Clinical Coordinators to facilitate the study and the timely collection of data.

e. Identification and enrollment of 100 NF2 patients (months 1-3); In Progress

Clinical Coordinators at each Patient Collection Center have screened their patient population and identified potential subjects for the NF2 Natural History study.

Table 1 below summarizes the current number of NF2 patients at each site who qualify for the study and are enrolled.

Table 1: Patient Enrollment

Patient Collection Center	Location	Total Identified	Patients Qualified	Patients Enrolled as of 9/13/00
House Ear Institute	Los Angeles, CA	308	47	43
MGH	Charlestown, MA	31	24	24
St. Mary's	Manchester, UK	64	23	14
Klinikum Nord Ochsensoll	Hamburg, Germany	20	11	11
Mt. Sinai Medical Center	New York, NY	11	3	1
Nagoya University: Kiyoshi	Nagoya, Japan	5	5	4
Total (Army Approved Sites)		439	113	97
Univ. Texas, Houston: Chang	Houston, TX	2	2	1*
Royal Victorian Eye and Ear Hospital: Briggs	Melbourne, Australia	13	7	5*
Ohio State Univ. Hospital: Welling	Columbus, OH	4	4	4*
Total (once all sites receive Army approval)		470	131	107*

*consented to enroll and will be enrolled post Army approval

"Total Identified" signifies patients whose chart were reviewed.

"Patients Qualified" signifies patients meeting inclusion criteria.

"Patients Enrolled" signifies consented patients.

The major problem of this study has been patient accrual due to the unanticipated delay of Institutional Review Board (IRB) approval for all sites and delay in the Army approval of the Single Project Assurance (SPA) for the foreign sites. See Appendix A for a chronology of the site approval process. The current status of IRB approval and Army approval is listed below.

Table 2: IRB approval dates for sites with full Army approval to enroll subjects.

Patient Collection Centers	IRB/Ethics Committee Approval	US Army Approval
House Ear Institute	February, 1998	December, 1998
MGH	March, 1999	June, 2000
Mt. Sinai	December, 1998	April, 2000
St. Mary's	February, 1999	March, 2000
Klinikum Nord Ochsensoll	January, 1999	April, 2000
Nagoya University	February, 2000	September, 2000
Royal Victorian Eye and Ear Hospital	March, 2000	Pending
Ohio State University	April, 2000	Pending
University of Texas, Houston	April, 2000	Pending

A second reason for the slower than expected enrollment is difficulty enrolling patients from the Mount Sinai Medical Center. Mount Sinai was expected to enroll upwards of 20 patients and thus far, one patient has been enrolled.

f. Collection of baseline individual patient data (months 2-6); In Progress

Baseline MRI data have been collected on 69 patients (71% of enrolled patients) and 62 baseline audiology examinations (64% of enrolled patients) have been performed. Baseline Clinical Exam data has been collected for 40 patients (41% of enrolled patients). Specifics of data collection are listed under tasks 2, 3, and 4.

g. Collection and computerization of yearly follow-up individual patient data (months 12-35); In Progress

HEI is in contact with each clinical coordinator, providing information on upcoming follow-up examinations to be scheduled. One-year follow-up audiology data has been collected on 17 patients, one-year follow-up radiology data has been collected for 20 patients, and 16 patients have completed one-year follow-up clinical exams. All follow-up data forms received have been entered into the NF2 database.

h. Preparation of US Army grant for future clinical treatment outcome study (months 25-36); Completed

Exisulind, a drug developed by Cell Pathways, Inc. has been identified as a candidate treatment for NF2. This drug has been highly effective in inhibiting growth of other neoplasms which have many similarities to NF2, in addition to an excellent safety profile. Unpublished studies at HEI have found Exisulind to inhibit growth and increase apoptosis of NF2 cell cultures. A Phase II treatment trial grant to treat NF2 patients with Exisulind has been prepared and submitted to the US Army on September 5, 2000.

i. Data editing, corrections, updates, and management (months 4-35); In progress

Data editing, corrections, and updating is an ongoing process as data are submitted. The clinical coordinators review the study data before forwarding it to the data management center at HEI. The HEI research assistant, data entry personnel, and/or a supervisor performs another review of the data. Clinical Coordinators are asked to re-submit any data that is problematic or to provide detailed information about any difficulties noticed in the data.

j. Data analysis (months 6-12, 22-24, 34-36); Pending

Data analysis will be performed when enrollment is complete. Initial analysis will include review of baseline and retrospective data.

k. Manuscript preparation (months 10-12, 22-24, 34-36); Pending

One manuscript describing the NF2 patients at the consortium centers entitled "Vestibular Schwannomas in Neurofibromatosis Type II: Research Considerations" has been presented at the American Academy of Otolaryngology and Head and Neck Surgery conference in September, 2000. This manuscript has been submitted for publication. Other manuscripts will be prepared once data analysis has been completed.

Task 2. *Standardized volumetric analysis of vestibular schwannomas using both retrospective and prospective radiographs.*

a. Development of standard operating procedure for digital analysis of MRIs (months 1-3); Completed

A standard operating procedure manual (SOP) is complete for both the Patient Collection Centers and the WorldCare Measurement Center. The WorldCare Patient Collection Center SOP was merged with the HEI procedure manual and has been distributed to the clinical coordinators at each Patient Collection Center.

b. Set-up for communication of data to the statistical analysis and data management center (months 1-3); Completed

There are two methods of data transfer to the Statistical Analysis and Data Management Center at HEI. All measurement data recorded on the WorldCare Measurement Center MRI data forms is transferred via mail and has also been emailed. All image data are transferred to HEI via FTP. HEI was provided with a viewing system for these FTP images complete with the measurement and viewing software Cheshire™.

c. Preparation of facilities at WorldCare, Inc. (months 1-3); Completed

A private suite for the NF2 Natural History Study has been prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data have been used for the collection and analysis of patient data. Also, the filing system, logbooks, and patient database are established to accept and track the workflow of patient data. An additional worksite has been set up next to the initial worksite to facilitate the radiologist reading the scans. The additional worksite has resulted in saving considerable time when transferring between images.

d. Preparation of MRI facility to transmit data (months 1-3); Initial Stage Completed, Additional Sites: Ongoing

Each of the MRI facilities affiliated with the original Patient Collection Centers has transmitted test data to WorldCare via optical disk or FTP. The initial task to certify a MRI facility at the original study sites is complete. As subjects were enrolled, the number of MRI facilities required to provide data have expanded. As stated in the study protocol, each MRI facility had to become familiar with the scanning protocol, agree to perform the scans as specified, and have their MRI equipment assessed for compatibility with WorldCare. To date, prospective data has been collected from 57 MRI sites. The process of certifying MRI facilities to send study data will be ongoing.

e. Collection of MRI scan obtained prior to initiation of study (months 2-6); In Progress

The five approved study sites have collected retrospective films from 174 separate patient visits and forwarded them to WorldCare. WorldCare has scanned these films in preparation for assessment and returned them to the study sites. The WorldCare technician and radiologist has reviewed 67 of the scanned films and provided both their linear and 3D volumetric measurements of acoustic neuromas and/or meningiomas on Case Record Forms. These forms have been sent to the Statistical Analysis and Data Management Center at HEI where it was entered into the study database.

f. Collection and Analysis of Baseline MRI (months 1-35); In Progress

Baseline MRI is defined as the first MRI completed after enrollment. Sixty-nine of the 97 enrolled subjects (71%) have completed their baseline scan. Of these, 20 are in the process of being collected from the study sites, 35 are in the process of being scanned and analyzed by WorldCare, and 14 have been received from WorldCare with linear and 3D volumetric measurements on Case Record Forms.

Twenty-four of the 97 enrolled patients are due for a baseline MRI in the future; all baseline evaluations should be completed by April 2001. Twenty-one of these 24 patients have enrolled recently (after 4/1/00), which accounts for the late baseline MRI evaluations. Three subjects will have their baseline scans during the next two months (October – November).

Four of the 97 patients are missing their Baseline MRIs. One did not have an MRI in 1999 and three others were enrolled after they had had an MRI. For these three patients, baseline audiology and clinical exams were completed soon after enrollment, but a corresponding prospective MRI could not be completed.

g. Collection of Yearly Follow-up MRI material (months 1-35); In Progress

Twenty enrolled subjects have completed their one-year follow-up scan. Of these, nine are in the process of being collected from the study sites, ten are in the process of being scanned and analyzed by WorldCare, and one has been received from WorldCare with linear and 3D volumetric measurements on Case Record Forms. Additionally, five subjects will have their one-year follow-up scan during the next two months (October-November).

h. Transmitting volumetric data to the statistical analysis and data management center (months 4-35); In Progress

Both measurement and image volumetric data for the first 84 evaluations (prospective and retrospective) reviewed have been transmitted from WorldCare to the Statistical Analysis and Data Management Center at HEI. The image data was transferred via FTP to a review station at HEI equipped with the measurement and viewing software Cheshire™. The measurement data for both the technician and radiologist were recorded on MRI data forms and sent via mail to HEI.

Task 3. Standardized prospective neurophysiological/audiological analysis of patients.

a. Training clinical centers on audiology protocol (months 1-3); Completed

The audiology protocol was distributed to the Patient Collection Centers and questions were directed to the Audiology Center Coordinator. Study audiologists have been identified at each of the patient collection centers that have agreed to conduct the examinations.

b. Development of communication pathways for audiology data management (months 1-3); Completed

The Statistical Analysis and Data Management/Coordinating Center at HEI manages the audiology data in the same manner as other study data. As outlined in the study Procedure Manual, completed forms are initially faxed to the HEI Research Assistant and the original is mailed to HEI at the end of each month. Once the Research Assistant receives the completed *Audiology Data Form*, it is forwarded to the Audiology Center Coordinator at HEI to be reviewed. The data are then entered into the database.

c. Collection of audiometric testing performed prior to initiation of study (months 2-6); In Progress

Retrospective audiological data have been collected from 355 different patient visits for the enrolled patients. Collection of retrospective data is an ongoing process due to delayed patient enrollment.

d. Collection of baseline audiometric data (months 2-6); In Progress

Baseline audiometric data for 62 subjects have been collected to date. Collection of baseline audiology data remains an ongoing process due to delayed patient enrollment. An additional 3 subjects have been scheduled for their baseline audiological examinations in the next 2 months.

e. Collection of follow-up yearly audiometric data (months 1-35) In Progress;

Follow-up audiometric data have been collected on 17 patients. Collection of one-year follow-up audiology data remains an ongoing process due to delayed patient enrollment. Five enrolled subjects will have their one-year follow-up audiology examination in the next two months.

Task 4. Examination of molecular, pathological and clinical features which may predict tumor behavior.

a. Standardization of methods for pathological and molecular analysis (months 1-3); Completed

A standard protocol and report has been established for review of pathological specimens and for the molecular genetic analysis.

b. Establish method of data acquisition and transfer to the statistical analysis and data management center (months 1-3); Completed

As outlined in the NF2 Natural History Procedure Manual, data are acquired and recorded on the data forms which are then faxed and mailed to House Ear Institute.

c. Collection of pathological samples from tumors removed prior to initiation of study for analysis (months 4-9); In Progress

For twenty-eight patients, it is assumed that no surgical resection of a tumor prior to enrollment has occurred. For the remaining sixty-nine enrolled patients with a tumor resection, thirty-six tumor specimens, including H & E slides, unstained slides, and pathology reports have been obtained. Collection of pathological samples from tumors removed prior to initiation of this study is an ongoing process, due to delayed patient enrollment.

All collected specimens have been stained for Ki-67 with MIB1 antibodies using positive and negative controls (tonsils). Image analyses have not yet been performed to quantitate the staining, but will be performed once additional cases have been received and stained.

The assay for Neurofilament antibodies to assess trapped nerve fibers is in the process of optimization. Data sheets will be filled out and sent to HEI once the staining has been completed and the slides have been reviewed by Dr. Louis and Dr. Stemmer-Rachamimov.

Blood for molecular analysis has been obtained from 61 patients. Tumor blocks for molecular analysis has been collected for 46 patients. Molecular analysis has been completed by Dr. MacCollin's lab on 41 subjects.

d. Collection of pathology samples from tumors removed during the course of the study (months 1-35); In progress

Two patients have had their second vestibular schwannomas resected during the course of the study and tumor samples have been collected. One patient underwent radiotherapy on a second vestibular schwannoma.

Key Research Accomplishments

- Development of an international consortium of clinical centers and expertise in NF2.
- Establishment of standardized study protocol for multi-institutional, multi-national natural history study.
- Development of NF2 specific database which includes clinical, radiographical, audiometrical, pathology, and molecular biology/genetic information.
- Development of standard operating procedure for digital analysis of MRIs utilizing information from a variety of MRI machines from different manufacturers.
- Establishment of NF2 specific pathology specimen bank.
- Development of NF2 molecular biology database.

Reportable Outcomes

-Initial Steering Committee Meeting, December 4, 1998

-Progress Report, April, 1999, submitted to USAMRMC

-Progress Report, October, 1999, submitted to USAMRMC

-Progress Report, April, 2000, submitted to USAMRMC

-Steering Committee Meeting, June 4, 2000:

Interim data on the progress of this study were reported. The data collection process and direction of Future data analyses were discussed by all Co-Principal Investigators.

-American Academy of Otolaryngology Head & Neck Surgery Meeting, September 24-27, 2000:

Treatment of Vestibular Schwannomas in Neurofibromatosis Type 2 , paper submitted prior to presentation.

-American Neurotology Society Meeting, May 12-13, 2001:

MRI Test-Retest of Vestibular Schwannoma in NF2, abstract submitted, paper to be submitted prior to Presentation.

Conclusions

The infrastructure necessary for this project to be successful has been assembled. Subject enrollment has been difficult due to the delay in achieving Army approval of the informed consent forms for each institution and for Army approval of the Single Project Assurance for the foreign sites. Additionally, a Co-Principal Investigator left one of the core patient collection sites. Despite these difficulties, baseline audiological data will be collected on 64% of the enrolled subjects and 71% of the subjects will have undergone their baseline MRI scans.

References:

1. Slattery, WH, Fisher, LM, and NF2 Natural History Consortium. Neurofibromatosis Type II: Research Considerations. *Otolaryngol Head Neck Surg*, submitted Sept 2000.

Appendix A

House Ear Institute:

2/1/98 Submitted informed consent form to IRB
 3/1/98 IRB approved informed consent form
 10/5/98 Approval for enrollment of subjects from Army
 2/24/99 IRB approval letter sent to Army Regulatory personnel (Cathy Smith)
 1/6/00 SPA re-submitted to Army Regulatory personnel (Maj. Miller)

Massachusetts General Hospital (MGH):

12/18/98 First draft of informed consent reviewed by Army Regulatory personnel (Kenna Conner) and comments returned
 2/19/99 Second draft of informed consent sent to Army Regulatory personnel
 3/17/99 MGH IRB approved informed consent
 4/5/99 IRB-approved, stamped informed consent sent to Army Regulatory personnel (Catherine Smith)
 7/7/99 IRB approval letter, stamped informed consent FEDEX to Army Regulatory personnel (Sonya Lewis)
 9/23/99 MGH received verbal approval from Army Regulatory personnel to begin enrolling subjects, contingent on making the revisions requested
 1/4/00 Multiple Project Assurance (MPA) information sent to Army Regulatory personnel (Maj. Bob Miller)
 3/16/00 Compromise reached with MGH IRB and Army, informed consent re-submitted to MGH IRB committee
 6/1/00 Completed approval of the site by the Army for patient enrollment

Mt. Sinai Medical Center:

12/4/98 Mt. Sinai IRB approval letter and stamped approved copies of the informed consent form sent to Army Regulatory personnel (Kenna Conner)
 1/13/99 Army's concerns about the informed consent sent to HEI
 3/17/99 After numerous attempts to contact Army Regulatory personnel, the second draft of the informed consent was sent to Army Regulatory personnel (Catherine Smith)
 3/24/99 Second informed consent draft sent to Army Regulatory personnel
 5/1/99 Mt. Sinai Principal Investigator leaves Mt. Sinai
 7/7/99 Third draft of informed consent and IRB approval letter FEDEX to Army Regulatory personnel (Sonya Lewis)
 9/27/99 The third informed consent draft was conditionally approved by Army Regulatory personnel, with revisions
 1/4/00 Multiple Project Assurance (MPA) information sent to Army Regulatory personnel (Maj. Bob Miller)
 1/6/00 Verbal approval of the informed consent by Army Regulatory personnel. Immediately requested site to submit to IRB.
 3/31/00 Complete approval of the site by the Army for patient enrollment

University of Texas, Houston:

11/10/99 Submitted informed consent to Army Regulatory personnel (Sonya Lewis)
 1/4/00 MPA number submitted to Army Regulatory personnel (Maj. Miller)
 1/6/00 Verbal approval of the informed consent by Army Regulatory personnel. Immediately requested site to submit to IRB.
 4/14/00 Revised informed consent faxed to Army for approval

Ohio State University:

1/4/00 MPA number submitted to Army Regulatory personnel (Maj. Miller)
 1/6/00 Verbal approval of the informed consent by Army Regulatory personnel. Immediately requested site to submit to IRB. Site did so.
 4/21/00 IRB approval with stipulations, wording changes to fit local requirements, not yet completely approved

FOREIGN SITES:

Klinikum Nord Ochsenzoll:

2/10/99 HEI received Ethics Committee approval letter and stamped informed consent, completed SPA

2/11/99 SPA faxed to Army Regulatory personnel (Catherine Smith)
2/24/99 Approval letter, informed consent, SPA FEDEX to Army Regulatory personnel
4/23/99 Certificate of Translation sent to Army Regulatory personnel
7/7/99 Ethics Committee approval letter, Certificate of Translation, consent forms, and SPA FEDEX to Army Regulatory personnel (Sonya Lewis)
9/24/99 Army Regulatory personnel requested changes to the Certificate of Translation
10/7/99 Finalized Certificate of Translation faxed to Army Regulatory personnel
1/6/00 3rd time SPA submitted to Army Regulatory personnel (Maj. Miller)
4/5/00 Complete approval from Army for patient enrollment

St. Mary's Hospital:

1/13/99 First draft of informed consent sent to Army Regulatory personnel (Kenna Conner)
1/26/99 Specimen donation language an issue to be resolved with the site
7/7/99 Ethics Committee approval letter, informed consent, SPA FEDEX to Army Regulatory personnel (Sonya Lewis)
1/6/00 Verbal approval from Army Regulatory personnel (Maj. Miller) of the informed consent. Immediately notified St. Mary's, asking them to re-initiate informed consent approval process. 2nd time SPA submitted to Army Regulatory personnel
4/5/00 Complete approval from Army for patient enrollment

Royal Victorian Eye and Ear (Melbourne):

10/7/99 Letter to Army Regulatory personnel (Sonya Lewis) regarding addition of Melbourne as an investigational site
11/8/99 Submitted informed consent to Army Regulatory personnel
12/9/99 Army requested revisions received
1/6/00 Verbal approval from Army Regulatory personnel (Maj. Miller) for the informed consent. Immediately requested the site submit to their IRB for approval
3/16/00 Sent SPA forms to Melbourne in anticipation of Army requiring those forms.
4/12/00 Faxed and FEDEXed SPA and IRB approval to Army

Nagoya University (Japan):

10/28/99 Submission of Nagoya as an additional site to Army personnel, as instructed (Kathy Dunn)
1/19/00 Informed consent and Certificate of Translation submitted to Army Regulatory personnel (Maj. Miller)
2/29/00 Letter from Dr. Winsor, Chair, St. Vincent's IRB sent to Army Regulatory personnel (Maj. Miller)
3/17/00 Informed consent, Ethics Committee approval letter, Certificate of Translation, SPA, FEDEX to Army Regulatory personnel
4/4/00 Detailed local IRB regulations to Army, requested approval of site
9/15/00 Complete approval from Army for patient enrollment